Overview: GMP, GTP and QS Regulation

Mary Malarkey
Director, Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
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Summary

- HCT/Ps that also meet the definition of a biological drug or a device
- Focus on how the CGMP, CGTP regulations and the QS regulation would be applied to these products
- Other regulatory requirements may also be applied (e.g. IDE and IND regulations)

Guiding Principles: CGTPs

- 21 CFR 1271.150(a)

This subpart D (GTPs) and subpart C (Donor Eligibility) of this part set forth current good tissue practice (CGTP) requirements. You must follow CGTP requirements to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (e.g., by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing).

CGTPs?

- 1271.150(a)
- Communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents.
- CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution.

Guiding Principles: CGMP

- Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FDCA) states that a drug shall be deemed adulterated if “the methods used in, or the facilities and controls used for, its manufacturing, processing, packing, or holding do not conform to or are not operated or administered in conformity with

CGMP

- ..**current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets quality and purity characteristics, which it purports or is represented to possess.”

NOTE

- For products that meet the definition of a drug under section 201(g) of the FDCA, the CGMP regulations apply regardless of application status*. This is also true for products that also meet the definition of a biological product under section 351(i) of the PHSA.

*except phase 1 IND products if DFR becomes effective

Current Good Manufacturing Practice (CGMP)?

- Regulations at 21 CFR Parts 210 and 211
- Applicable to preparation of drug **products** for administration to humans and animals, including phase 2 and 3 clinical trials*
- GMPs cover manufacturing, controls, testing and documentation
- CGMP - the “C” means current - GMPs are minimal standards.

* except phase 1 IND products if DFR becomes effective

Drug substance or intermediate production

- What is the difference between a drug product and a drug substance?
- Production of the drug product refers to the preparation of the finished dosage form, so processes leading up to that point produce intermediates or drug substances that are not specifically covered under Parts 210-211
- HOWEVER, the statutory GMP is applied, similar expectations (ICH Q7A).

Guiding Principles: Quality System Regulation

- Section 501(h) of the Federal Food, Drug and Cosmetic Act states a device will be deemed adulterated if “the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with applicable requirements under section 520(f)(1) or an applicable condition prescribed by an order under section 520(f)(2).”

Section 520(f)(1)

- States that the Secretary may “prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, pre-production design validation (including a process to assess the performance of a device but not including an evaluation of the safety or effectiveness of a device), packing, storage, and installation of a device conform to current good manufacturing practice, as prescribed in such regulations, to assure that the device will be safe and effective and otherwise in compliance with this Act.”

QS Regulation Implements Section 520(f)

- Regulations in Part 820.
- Govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation and servicing of all finished devices intended for human use.

QS Regulation?

- Requirements intended to ensure that finished devices will be safe and effective and otherwise in compliance with the FDCA
- Finished device manufacturer responsible to establish and maintain requirements, including quality system requirements, that must be met by suppliers, contractors and consultants.

Conforming amendments

- ✓ 21 CFR 1271.150(d); (820.1(a)(1))

Compliance with parts 210, 211, and 820 of this chapter. With respect to HCT/Ps that are drugs (**subject to review** under an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act or under a biological product license application under section 351 of the Public Health Service Act) or that are devices (subject to premarket review or notification under the device provisions of the act or under a biological product license application under section 351 of the Public Health Service Act), the procedures contained in this subpart and in subpart C of this part and the current good manufacturing

practice regulations in parts 210 and 211 of this chapter and the quality system regulations in part 820 of this chapter supplement, and do not supersede, each other unless the regulations explicitly provide otherwise.

In the event that a regulation in part 1271 of this chapter is in conflict with a requirement in parts 210, 211, or 820 of this chapter, the regulations more specifically applicable to the product in question will supersede the more general.

What does this mean?

- **Due to the broader scope of these regulations, most of the CGMP regulations under Parts 210 and 211 would be applicable for HCT/Ps that are not regulated solely under section 361 of the PHSA and meet the definition of drugs in the FDCA and biologics in the PHSA.**

What does this mean?

- **Due to the broader scope of these regulations, most of the QS Regulation under Part 820 would be applicable for HCT/Ps that are not regulated solely under section 361 of the PHSA and meet the definition of devices in the FDCA.**

Broader in Scope?

- CGMP
  - Address safety, purity, potency, and quality of the drug product;
  - Potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect the given result
- QS Regulation
  - Address safety and effectiveness

Broader in Scope?

- CGTPs address transmission of communicable disease, which is one issue related to safety; however, other safety concerns may be present due to, for example, the purity or quality of the drug product
- Therefore, for the most part, the CGMPs or QS Regulation would be applied and the CGTPs subsumed under the broader CGMP or QS Regulation requirements
- Compliance with these CGMP or QS Regulation requirements would mean compliance with CGTP requirements

Would any GTPs apply?

- YES, again, all apply but most subsumed by the broader GMPs or QS Regulation. Which GTPs would be applicable and must be followed?:
  - Subpart C: Donor eligibility requirements are unique to the GTPs and would be applied

Prevention of the Introduction, Transmission, or Spread of Communicable Disease

- 1271.145 – You must recover, process, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in a way that prevents the introduction, transmission of spread of communicable diseases.

Compliance with applicable requirements

- 1271.150(c) – Before entering into a contract, agreement or other arrangement…you must ensure that the other establishment complies with applicable CGTP requirements.
- If you become aware of information suggesting that the establishment is not in compliance with such requirements:
  - Take reasonable steps to ensure compliance with requirements
  - Terminate your contract, agreement or other arrangement

Exemptions and alternatives

- 21 CFR 1271.155
  - Those relating to Subpart C; Donor Eligibility
  - May be considered for those relating to provisions in Subpart D, taking into account the corresponding CGMP r QSR
  - 1271.155 (b) – (g) describe the procedures for requesting an exemption or alternative; criteria for granting such a request; operating under and properly documenting once granted and issuance in a public health emergency.

Quality Program

- 21 CFR 1271.160(b)(2)
- Having procedures for sharing information pertaining to possible contamination or potential for transmission of communicable disease with other establishments:
  - Known to have recovered from same donor
  - Known to have performed manufacturing steps with respect to the same HCT/P

- 21 CFR 1271.160(c)
  - Audits – as defined in 1271.10(gg) for core GTPs;
  - Relating to communicable disease transmission
  - Required for core GTPs such as donor eligibility
  - Could be performed more broadly for the corresponding CGMPs to satisfy the requirement;

Quality Audits – QS Regulation

- 820.22 – For HCT/Ps that are also devices; quality audits of the quality system requirements in Part 820 Subpart B would also be required

What about the other GTP Quality Program requirements vs CGMP?

- ✓ Limited to procedures governing core GTPs
- ✓ The GMPs provide for a Quality Control Unit that has broad responsibility
- ✓ This responsibility is described under 21 CFR 211.22
- ✓ Also interspersed throughout the GMP regulations

Quality Control Unit
21 CFR 211.22

- Responsibility and authority to approve/reject all components, in-process materials, packaging, labeling and drug products and authority to review records to assure no errors have occurred and if occur; fully investigated; including contract operations.
- Responsibility to approve/reject procedures/specifications impacting on identity, strength, quality, and purity of the drug product
- Adequate laboratory facilities for testing
- Responsibilities and procedures in writing

Additionally

- 21 CFR 211.100
  - Production and process controls procedures (process validation), including changes ..reviewed and approved by the QCU.
- 21 CFR 211.160
  - Establishment of specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including changes to any…reviewed and approved by the QCU

Additionally

- 21 CFR 211.192 – Production Record Review
  - All drug product production and control records…shall be reviewed by the QCU to determine compliance with all established, approved, written procedures before a batch is released or distributed. Any discrepancies must be thoroughly investigated .

Additionally

- 21 CFR 211.198 - Complaint Files
  - Written procedures established and followed, including provisions for review by the QCU of any complaint related to drug product failures; need for investigation; need to evaluate whether represents and adverse drug experience and, if so, reported properly


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What about the other GTP Quality Program requirements vs QS Regulation?

- Limited to procedures governing core GTPs
- The QS Regulation provides for each manufacturer to establish and maintain a quality system appropriate for the device and in compliance with Part 820
- *Quality System* is defined in 820.3(v) as the organizational structure, responsibilities, procedures, processes and resources for implementing quality management

“Establish and Maintain” and “Where Appropriate”

- 820.3(k) Establish means define, document (in writing or electronically), and implement.
- 820.1(a)(3) When a requirement is qualified by ``where appropriate,'' it is deemed to be ``appropriate'' unless the manufacturer can document justification otherwise. A requirement is ``appropriate'' if nonimplementation could reasonably be expected to result in the product not meeting its specified requirements or the manufacturer not being able to carry out any necessary corrective action.

“Establish and Maintain” and “Where Appropriate”

- 1271.3(cc) Establish and maintain means define, document (in writing or electronically), and implement; then follow, review, and, as needed, revise on an ongoing basis.
- 1271.150(e) When a requirement is qualified by ``where appropriate,'' it is deemed to be ``appropriate'' unless you can document justification otherwise. A requirement is ``appropriate'' if nonimplementation of the requirement could reasonably be expected to result in the HCT/P not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable diseases, or in your inability to carry out any necessary corrective action.

Subpart B: Quality System Requirements

- 820.20 Management Responsibility – establish and maintain:
  - Quality policy
  - Organization
    - Responsibility and authority
    - Resources
    - Management representative
  - Management review
  - Quality planning
  - Quality system procedures

Subpart B: Quality System Requirements

- 820.22 – Quality Audits- previously discussed
- 820.25 – Personnel

GTPs that would be applicable

- Processing and process controls
- 21 CFR 1271.220(b)
  - Pooling – Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.
- 21 CFR 1271.220(d) Dura mater (not likely)
- GMPs/QS Regulation applicable to other production and processing controls: process validation, in-process testing, change control, as apply to identity, strength, quality and purity/ safety and effectiveness

Examples of GTP vs. GMP

- 21 CFR 1271.265 – some distinctions from or complement to 211 requirements:
- (a) Receipt procedures for HCT/Ps; requires evaluation of incoming HCT/Ps with respect to presence of microorganisms, damage and contamination. Decision to accept, reject or quarantine.
- 21 CFR 211.84(a) requires procedures in sufficient detail for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components

- Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the drug product.
- Very broad in scope; covers incoming HCT/P for further manufacture as well as components used in manufacture (i.e. supplies and reagents under 21 CFR 1271.

Examples of GTP vs. QS Regulation

- 21 CFR 1271.265 – some distinctions from or complement to 820 requirements:
- (a) Receipt procedures for HCT/Ps; requires evaluation of incoming HCT/Ps with respect to presence of microorganisms, damage and contamination. Decision to accept, reject or quarantine.
- 21 CFR 820.50 Purchasing Controls; requires establishment and maintenance of procedures to ensure that all purchased or otherwise received product and services conform to specified requirements

- 21 CFR 1271.265 (b) Predistribution shipment
  - Distinctive in GTPs as specifically addresses shipment of HCT/Ps prior to release for distribution.
  - Would be applied

- 21 CFR 1271.265(c) Availability for distribution
  - (1) covered by 211.22, 211.165, 211.167, 211.192; 820.40, 820.86; 820.90; 820.100; 820.160
  - (2) specific to review of donor eligibility; so would be applied
  - (3) covered under 211.192; 820.90; 820.100

(d) specific to packaging and shipping of HCT/Ps; so would be applied

- 21 CFR 1271.265(c) – Availability for distribution
  - (e) – requirements for procedures for documentation of release and distribution covered under GMPs and QS Regulation
  - (f) – return to inventory covered under 211.204; and 820.140 and 820.150

Records

- 21 CFR 1271.270
  - (a) – (c) – covered under GMPs and QS Regulation 211.180, 211.188; 820.40; 820.180
  - (d) requires retention of records for 10 years; so would be applied
  - (e) – records of all contracts and agreements; not required under GMP; so would be applied. Covered under 820.50 (purchasing controls) so would not be applied for HCT/Ps that are devices

Tracking

- 1271.290
- Tracking – (a) – (g) – distinctive to HCT/Ps in tracking requirements, distinctive codes; relating to donor ; so would be applicable
- CGMP and QS Regulation requirements not as specific. CGTP would be applied

CGMP Subparts: Would be applied for the most part

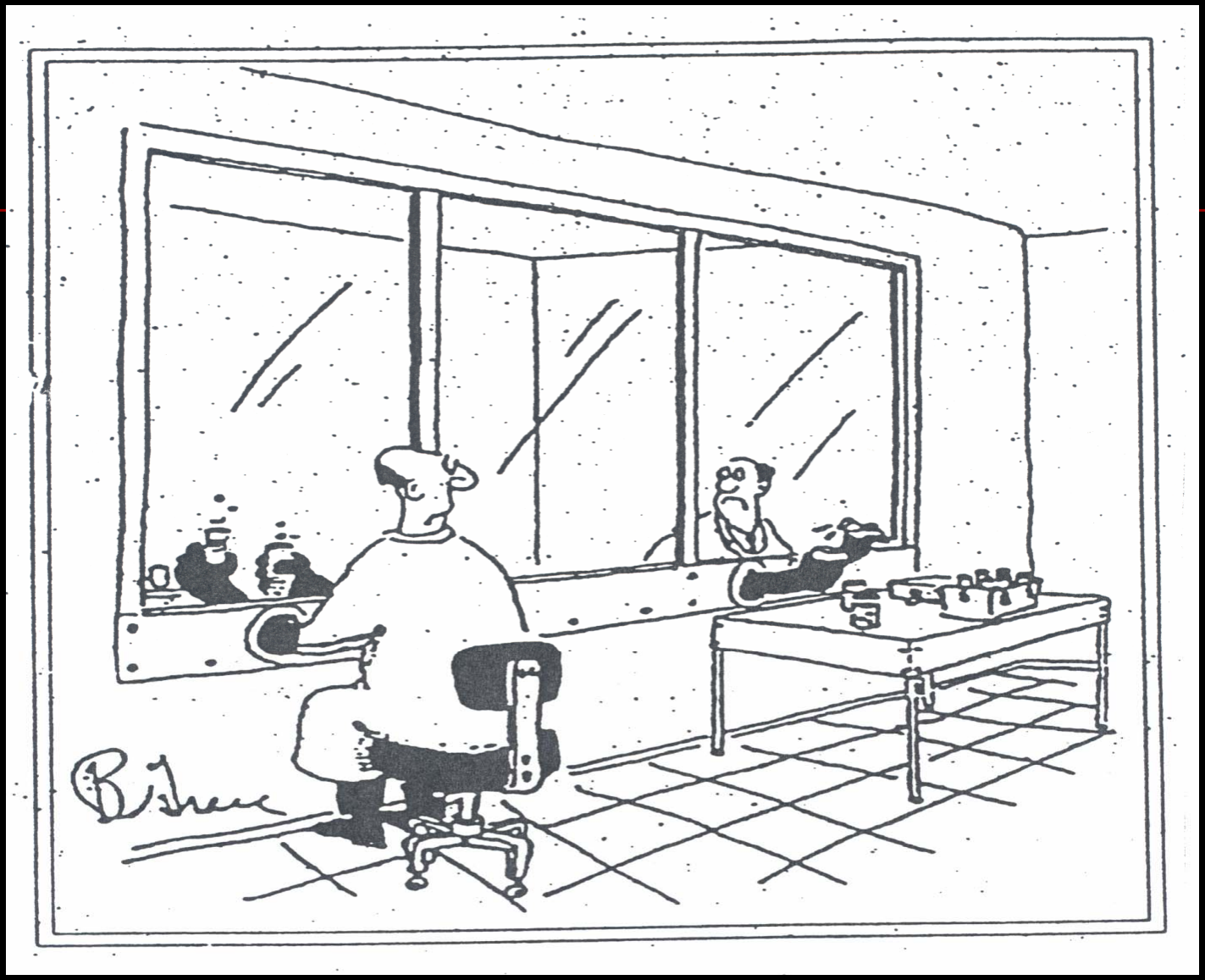
- ✓ Organization and personnel
- ✓ Building and facilities
- ✓ Equipment
- ✓ Control of Components
- ✓ Production and Process Controls
- ✓ Packaging and Labeling Control
- ✓ Holding and Distribution

CGMP Subparts:

- ✓ Laboratory Controls
- ✓ Records and Reports
- ✓ Returned and Salvaged Drug Products

GMP vs. GTP?

- It is most likely that the majority of cord blood, hematopoietic stem cell and DLI facilities are working in both GTP only and GTP/GMP mode.
- Exception – facilities doing only autologous or first- or second- degree blood relative.
- From a facility, environmental control and cleaning perspective, the requirements are very similar; as freedom from contamination is the driving force for these requirements in both cases.



Considerations

- Exposure of product during processing; should be in controlled environment
- Use and validation/verification of “closed” systems
- Elimination of practices that would be considered unacceptable under either regulatory scheme, regardless of facility classification
  - Example: Processing multiple donor cells at the same time

QS Regulation vs. GTP?

- The same is true
- Environmental controls and contamination controls under the QS Regulation address these same issues

QS Regulation Subparts: Would be applied for the most part

- Quality System Requirements
- Design Controls
- Document Controls
- Purchasing Controls
- Identification and Traceability
- Production and Process Controls
- Acceptance Activities

QS Regulation Subparts

- Nonconforming Product
- Corrective and Preventive Actions
- Labeling and Packaging Control
- Handling, Storage, Distribution and Installation
- Records
- Servicing

QS Regulation Subparts

- Depending on the nature of the device, the installation and servicing requirements may or may not be applied
  - Example: demineralized bone mixed with a carrier that would constitute a finished device would not be a device subject to these requirements.

Are CGMPs applicable while under IND?

- YES;
- 21 CFR 312.23(a)(7)
- Must assure proper identification, quality, purity and strength of the investigational product
- Amount of information will vary with the phase of the investigation, the proposed duration, the dosage form and amount of information otherwise available

Are CGMPs applicable while under IND?*

- Examples:
- FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses.
- Final specifications are not expected until the end of the investigational process

* except phase 1 IND products if DFR becomes effective

Is the QS Regulation applicable while under IDE?

- 21 CFR 812.1 exempts devices with an approved IDE from section 520(f) of the FFDCA except for the Design Control requirements in 820.30 unless the sponsor states an intention to comply with these requirements.

Conclusion

- For HCT/Ps that also meet the definition of a biological drug or a device, the 1271s do apply; however, many would be subsumed under the 211 or 820 requirements as these requirements are broader in scope.
- Compliance with 211 or 820 requirements would mean compliance with the 1271s that are subsumed.